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# Treatment of dMMR Metastatic Colorectal Cancer in 2025

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## Introduction

Deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC), accounting for approximately 4–5% of cases, represents a distinct molecular subgroup with unique therapeutic implications.[1] These malignancies are characterized by a high mutational burden and increased immune cell infiltration, making them particularly responsive to immune checkpoint inhibitors (ICI).[2] Conversely, this subgroup tends to be less sensitive to traditional chemotherapy.[3]

## ICI in mCRC

Programmed cell death protein 1 (PD-1) blockade initially demonstrated success in many refractory malignancies. However, in one of the early studies, only one out of 33 patients with mCRC responded to treatment.[4] Notably, this patient had a dMMR tumour. This pivotal observation led to extensive clinical trials evaluating PD-1 inhibitors, either alone or in combination with a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor (ipilimumab), in dMMR mCRC.[5-9] These studies ultimately established immunotherapy as the cornerstone of treatment for this molecular subtype.

As with most oncology drugs, ICI were initially studied in refractory dMMR mCRC. Following remarkable responses and the emergence of long-term survivors, their efficacy was subsequently evaluated in the first-line setting, leading to a paradigm shift in the management of dMMR mCRC. The first major clinical trial to draw global attention to immunotherapy in mCRC was the non-randomized Phase II KEYNOTE-016 study.[5] This trial evaluated the efficacy of pembrolizumab (PD-1 inhibitor; 10 mg/kg every 14 days) in three small patient cohorts: 10 patients with dMMR mCRC, 18 with proficient mismatch repair (pMMR) mCRC, and 7 with dMMR non-CRC malignancies. Among patients with dMMR mCRC, the overall response rate (ORR) was 40%, and the 20-week immune-related progression-free survival (PFS) rate was 78%. In contrast, no responses were observed in pMMR mCRC, and only 11% of patients remained progression-free at 20 weeks.

Nivolumab, another PD-1 inhibitor, demonstrated significant activity as monotherapy in one of the Phase II CheckMate-142 trial cohorts. In this cohort, 74 patients with dMMR mCRC, including 53 who had received at least one prior line of systemic therapy, were treated with nivolumab (3 mg/kg every 2 weeks). The study reported an ORR of 31.1% and a disease control rate (DCR) of 69%, with eight patients experiencing responses lasting over a year.[10]

Another cohort within the CheckMate-142 trial explored the combination of nivolumab (3 mg/kg) with ipilimumab (1 mg/kg) administered every 3 weeks for four doses, followed by nivolumab monotherapy every 2 weeks in 119 patients with refractory dMMR mCRC. This combination achieved an ORR of 55%.[11] The study further expanded to include a cohort of 45 patients, evaluating the dual ICI regimen of nivolumab and ipilimumab as first-line therapy in dMMR mCRC. Unlike the refractory setting, ipilimumab was administered at 1 mg/kg every 6 weeks, resulting in an ORR of 69% and a DCR of 84%.[7] While direct comparisons between these cohorts are challenging, two noteworthy observations emerge. The addition of ipilimumab to nivolumab appeared to enhance the ORR, suggesting a synergistic effect in dMMR mCRC. Additionally, the modified dosing schedule of ipilimumab (1 mg/kg every 6 weeks) in the first-line setting was associated with fewer severe adverse events, indicating a more tolerable safety profile.

The multicenter KEYNOTE-177 trial was the first Phase III study, enrolling 307 participants, to demonstrate a statistically significant and clinically meaningful improvement in PFS with

pembrolizumab compared to investigator's choice of chemotherapy in the first-line treatment of MSI-H/dMMR mCRC. At final analysis, the median PFS was 16.5 months with pembrolizumab versus 8.2 months with chemotherapy (hazard ratio [HR]: 0.59). The ORR was also higher in the pembrolizumab arm (45.1% vs. 33.1%), with responses being more durable, and therapy was associated with a more favourable toxicity profile. Although the median overall survival (OS) was numerically longer with pembrolizumab (not reached vs. 36.7 months with chemotherapy), it did not reach statistical significance. This may have been influenced by a high crossover rate (60%) from chemotherapy to immunotherapy.[12]

## Therapy Resistance

An important finding of the KEYNOTE-177 trial was that approximately one-third of patients in the pembrolizumab arm experienced disease progression within the first three months of treatment. The survival curves showed an early crossing, suggesting that a subset of patients initially fared better on chemotherapy than on pembrolizumab monotherapy. This raises the question of whether combining chemotherapy with ICI could help overcome this early resistance. This hypothesis is currently being tested in ongoing Phase III trials, such as the COMMIT study[13], which is investigating atezolizumab (an anti-programmed cell death ligand 1 [PD-L1] monoclonal antibody) as monotherapy versus a combination of FOLFOX (folinic acid, fluorouracil, and oxaliplatin), bevacizumab, and atezolizumab as first-line therapy for dMMR mCRC.

Until recently, the only evidence suggesting that the addition of ipilimumab (anti-CTLA-4) to an anti-PD-1 agent could partially mitigate primary resistance to single-agent PD-1 blockade came from the first-line cohort of the Phase II CheckMate-142 trial.[10] However, given the non-randomized nature of this trial, it was not possible to definitively conclude that dual ICI therapy was superior to PD-1 blockade alone.

This paradigm has now shifted with the recent data publication of the Phase III CheckMate 8HW trial, marking a significant milestone in the evolution of treatment strategies for dMMR mCRC.14,15 In this study, patients with dMMR mCRC, irrespective of the number of prior lines of therapy, were randomly assigned in a 2:2:1 ratio to one of the following treatment arms: **1)** nivolumab 240 mg plus ipilimumab 1 mg/kg every three weeks for four doses, followed by nivolumab 480 mg every four weeks (n=353); **2)** nivolumab 240 mg every two weeks for six doses, followed by nivolumab 480 mg every four weeks (n=354); or **3)** the investigator's choice of doublet chemotherapy (FOLFOX or FOLFIRI [folinic acid, fluorouracil, and irinotecan]), with or without bevacizumab or cetuximab (n=132). The dual independent primary endpoints were PFS for nivolumab plus ipilimumab versus chemotherapy (in the first-line setting) and PFS for nivolumab plus ipilimumab versus nivolumab monotherapy (across all lines of therapy) in patients with dMMR mCRC.

A total of 303 patients who had not previously received systemic treatment for their metastatic disease were included in the first phase of the analysis. The median PFS was not reached in the ICI arm, compared to 5.8 months in the chemotherapy arm (HR: 0.21; p<0.0001). Additionally, the incidence of grade 3–4 treatment-related adverse events (TRAEs) was lower in the ICI arm than in the chemotherapy group.

In the second phase of the analysis, 707 patients were randomized to receive either nivolumab plus ipilimumab or nivolumab monotherapy, regardless of prior lines of therapy. The combination of both ICIs resulted in a significant improvement in median PFS, which was not reached in the combination arm compared to 39.3 months in the nivolumab monotherapy arm (HR: 0.62, p=0.0003). Additionally, the ORR was 71% in the dual ICI arm compared to 58% in the nivolumab monotherapy arm, with 30% and 28% having complete responses, respectively. However, those benefits were accompanied by a slightly higher incidence of grade 3 or 4 TRAEs (22% vs. 14%). Further follow-up of the CheckMate 8HW trial is eagerly anticipated, particularly regarding OS outcomes. A summary of these findings and key results from other pivotal trials in MSI-H/dMMR mCRC is provided in **Table 1**.

In nearly all clinical trials evaluating ICIs, the therapeutic benefit of immunotherapy has remained consistent across various subgroups, irrespective of *BRAF* or *RAS* mutation status, the presence of Lynch syndrome, or the sites of metastases. This consistency underscores the broad applicability of ICIs in the treatment of dMMR mCRC, independent of underlying molecular or clinical characteristics.

| Study (*Year*) | Phase | N | Population | Arms | Median OS | Median PFS | ORR | Grade 3–4 TRAEs |
|---|---|---|---|---|---|---|---|---|
| KEYNOTE-016 Cohort A (CRC) (2015)[5,22] | II | 41 | Refractory MSI-H/dMMR CRC | PEMBRO 10 mg/kg q14d | 80.8 (95% CI: 33.2-NE) | 38.8 (95% CI: 8.1–NE) | 56.1% | 41% |
| CheckMate-142 First-line Cohort (2021)[7] | II | 45 | Untreated MSI-H/dMMR mCRC | IPI 1 mg/kg q6w + NIVO 3 mg/kg q2w | Not reached | Not reached | 69% | 22% |
| CheckMate-142 Refractory Cohort (2017)[10] | II | 74 | dMMR/MSI-H mCRC with ≥1 prior lines of therapy | NIVO 3 mg/kg q2w | Not reached | 14.3 mo; 95% CI: 4.3 – NE | 31.1% | 21% |
| KEYNOTE-177(2022)[12] | III | 307 | Untreated MSI-H/dMMR mCRC | PEMBRO 200 mg/q3w vs. CT | NR vs 36.7 mo; HR: 0.74; 95% CI: 0.53-1.03; P= 0.036 | 16.5 mo vs 8.2; HR: 0.59; 95% CI: 0.45–0.79 | 45% vs. 33% | 21.6% vs. 67.1% |
| CheckMate 8HW NIVO + IPI vs. CT (2024)[14] | III | 303 | MSI-H/dMMR mCRC | IPI 1 mg/kg + NIVO 240 mg q3w for 12 w followed by NIVO 480 mg q4w vs. CT | Not reported | NR (95% CI: 34.3–NE) vs. 6.2 mo (95% CI: 4.7–9.0) | Not reported | 23% vs. 48% |
| CheckMate 8HW NIVO + IPI vs. NIVO (2025)[15] | III | 707 | MSI-H/dMMR mCRC | IPI 1 mg/kg + NIVO 240 mg q3w for 12 w followed by NIVO 480 mg q4w vs. NIVO 240 mg q2w for 12 w followed by NIVO 480 mg q4w | Not reported | NR vs. 39.3 mo; HR: 0.62; 95% CI: 0.48–0.81; P=0.0003 | 71% vs. 58% | 22% vs. 14% |

**Table 1.** Key results from pivotal ICI trials in MSI-H/dMMR mCRC; *courtesy of Renata D'Alpino Peixoto, MD, PhD, and Thiago Miranda do Amaral, MD.*

**Abbreviations: CI:** confidence interval; **CT:** investigator's choice of chemotherapy; **dMMR:** deficient mismatch repair; **DOR:** duration of response; **HR:** hazard ratio; **IPI:** ipilimumab; **mCRC:** metastatic colorectal cancer; **mo:** months; MSI-H, microsatellite instability-high; **ne:** not evaluable; **NIVO:** nivolumab; **NR:** not reached; **OS:** overall survival; **PD-1:** programmed cell death protein 1; **PEMBRO:** pembrolizumab; **PFS:** progression-free survival; **TRAEs:** treatment-related adverse events; **w:** weeks.

## Remaining Questions for Immunotherapy use in dMMR mCRC

Several unanswered questions remain regarding the optimal use of ICIs in dMMR mCRC, including the ideal treatment duration. In pivotal clinical trials, patients with mCRC who do not experience disease progression or unacceptable toxicities typically receive ICIs for up to two years, after which treatment is discontinued. An observational cohort study involving 757 patients with dMMR mCRC treated with immunotherapy found that continuing treatment beyond two years did not improve OS. Furthermore, for patients who achieved a complete response, discontinuation of therapy after one year was not associated with any detrimental impact on OS.[16]

Another important consideration is the optimal therapy sequencing in patients with both dMMR and *BRAF*-mutated tumours. Approximately one-third of dMMR mCRC cases harbour the *BRAF* V600E mutation, often arising due to *MLH1* promoter hypermethylation. Despite the recent positive results from the Phase III BREAKWATER trial, which demonstrated that adding encorafenib and cetuximab to FOLFOX in the first-line setting improved ORR and OS compared to standard chemotherapy in patients with pMMR *BRAF* V600E-mutated mCRC, most oncologists would prioritize ICIs for patients who are also dMMR.[17] This preference is driven by the efficacy of ipilimumab plus nivolumab, which has been shown to induce complete responses in 30% of patients and provide durable responses. In such scenarios, the combination of FOLFOX, cetuximab, and encorafenib, as investigated in the BREAKWATER trial, could be considered in the second-line setting. Alternatively, encorafenib plus cetuximab, in alignment with the findings from the BEACON trial, may also represent a reasonable treatment option.[18] Nonetheless, future clinical trials evaluating the role of combining *BRAF* inhibitors with cetuximab or panitumumab and ICIs would be highly informative.

Another unresolved question pertains to the potential benefit of adding an anti-CTLA-4 agent in patients who have progressed on single-agent anti-PD-1 or anti-PD-L1 therapy. There is a strong biological rationale supporting this approach. CTLA-4 primarily regulates T-cell activation during the initial immune response, whereas PD-1/PD-L1 signaling predominantly suppresses T-cell activity within the tumour microenvironment. Combining anti-CTLA-4 with anti-PD-1 ICI may help overcome adaptive resistance mechanisms that emerge with anti-PD-1 monotherapy, thereby restoring immune activity against tumour cells. Some case reports have documented instances in which anti-PD-1 therapy had previously failed, but therapy response was recorded when ipilimumab was added to the regimen.[19,20]

Another critical issue is the potential for false-positive dMMR results in local laboratory testing. Studies have indicated that up to 60% of patients who exhibit disease progression on their first imaging evaluation during immunotherapy were subsequently found to be false-positive for dMMR based on local laboratory assessments. This highlights the necessity of centralized confirmation of MMR status to ensure accurate patient selection for immunotherapy.[21]

## Future Directions

Several novel strategies are currently under investigation to enhance the efficacy of ICIs in dMMR mCRC. These include combinations of ICIs with other ICIs, cytotoxic chemotherapy, monoclonal antibodies, targeted therapies, or novel agents. Additionally, ICIs are being incorporated into earlier stages of colorectal cancer treatment and are undergoing evaluation in neoadjuvant and adjuvant settings.

At present, pembrolizumab is approved across Canada for the first-line treatment of dMMR mCRC. However, while the approval of ipilimumab and nivolumab in this setting appears likely, it remains uncertain. Despite the clear clinical benefits associated with the addition of ipilimumab to nivolumab, this does need to be carefully balanced against increased toxicity and costs.

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## Financial Disclosures

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